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Reduced kidney size in patients with simple renal cysts

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Background. Renal cysts frequently occur in the absence of genetic diseases but their significance is unknown. Since multiple cysts develop in many patients with advanced renal disease, we tested the hypothesis that isolated cysts are associated with early nephron loss.

Methods. All inpatient and outpatient sonograms performed by the Renal Division since 1995 were reviewed and, after exclusion of duplicate studies, patients with genetic cystic disorders, complex cysts, hydronephrosis, peripelvic cysts, end-stage renal disease and transplanted kidneys, 2526 were selected for this study, of which 385 had one or more cysts. Maximum renal length was used as an indication of size, and renal function was estimated by serum creatinine concentration.

Results. Both right and left kidney length were significantly less in patients with cysts ($P < 0.0001$), independent of which kidney contained the cyst(s). Renal lengths were less in patients with multiple cysts as opposed to single cysts but not in patients with bilateral cysts as compared to unilateral cysts. Cysts were twice as frequent in solitary kidneys than in dual kidneys ($P = 0.01$). In outpatients matched for age and gender, those with cysts had a higher serum creatinine concentration but with borderline significance ($P = 0.06$). Multivariate analysis revealed that age, gender, and renal length were each independent variables and together accounted for one third of the incidence of cysts.

Conclusion. Kidney size is reduced in patients with simple renal cysts noted on renal sonography, and cysts may be associated with reduced renal function. This suggests that isolated cysts are an indication of nephron loss in patients with renal abnormalities.

Simple cysts are the most common structural abnormality observed in human kidneys. In some cases, cysts are abundant and the manifestation of a recognized genetic disorder such as autosomal-dominant polycystic kidney disease, tuberous sclerosis, and von Hippel-Lindau disease. In most cases, however, only one or two cysts are present and are not part of a recognized genetic disorder. Unless they exhibit some complexity, these "sporadic" or "acquired" cysts are largely ignored and their significance remains unknown. One exception is the frequent development of multiple cysts in kidneys of patients with end-stage renal disease, a disorder that has been termed acquired cystic kidney disease (ACKD) and is a risk factor for renal cell carcinoma. Despite identification of the genes responsible for most of the genetic cystic disorders, the pathophysiology of cyst formation is poorly understood and even less is known about acquired cysts. Specifically, it is not known whether acquired cysts are associated with any other parenchymal changes. The incidence of cysts increases markedly with age [1–5] but whether this is related to the loss of renal parenchyma that occurs with aging [6–9] is unknown. Compensatory hypertrophic or hyperplastic stimulation resulting from nephron loss [10] could induce cyst formation through aberrant tubular growth [11, 12]. The development of ACKD in advanced renal failure [13] is consistent with this hypothesis but the possibility that early nephron loss can lead to cysts formation has not been considered. Neither renal function nor size has been measured in any previous studies of cysts in patients without advanced renal failure. The greater incidence of simple renal cysts in males [1, 3–5] may also be linked to a greater growth stimulus since acquired cystic disease and renal carcinoma are both more frequent in males [14, 15].

The hypothesis that cyst formation is related to nephron mass was tested by correlating the incidence of cysts with kidney length in 2526 renal sonograms performed in both the inpatient and outpatient settings. In addition, serum creatinine concentration was compared in outpatients with and without cysts.

METHODS

Patients

Patients were selected from a database containing all renal sonograms performed by the Renal Division between August 1995 and October 2002. Of the 6308 studies, 3912 were performed on native kidneys, either in Emory University Hospital (inpatients) or the Emory Clinic (outpatients). Patients with end-stage renal disease (dialysis or transplantation) were excluded as were

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patients with a history or family history of genetic cystic disorders (autosomal-dominant polycystic kidney disease, tuberous sclerosis, and von Hippel-Lindau disease). In the case of repeat studies, all but the earliest study were excluded. Studies showing hydronephrosis, complex cysts, solid masses, or peripelvic cysts in either kidney, or crossed fused ectopia were also excluded. Analysis was performed on the remaining 2526 studies, of which 82 involved solitary kidneys and were analyzed separately.

Sonographic data

All sonograms were performed by nephrology trainees or one of two staff nephrologists with extensive experience in sonography. Renal trainees had received prior training in sonography and were supervised by the staff nephrologists, who interpreted all the studies. Simple cysts were identified on the basis of standard sonographic parameters: lack of internal echoes, thin wall, and distal enhancement. Maximal length of each kidney was determined from several measurements obtained from longitudinal images obtained in sagittal or coronal planes, or planes in between. These parameters were entered into the database at the time of the original interpretation and were used for this study without any reinterpretation or remeasurement.

Clinical data

Certain clinical data were entered into the database at the time of the sonogram, including age, gender, patient location, and indication for the sonogram. Serum creatinine concentration and results of additional radiology studies were obtained by chart review. For inpatients, we obtained the baseline serum creatinine concentration, defined as the lowest value for the hospitalization during which the sonogram was performed. Outpatients were assumed to have relatively stable renal function, and the measurement closest to the date of the sonogram was selected provided it was within 3 months.

Data analysis

Patient selection was performed on the original database, written in FileMaker Pro (FileMaker, Inc., Santa Clara, CA, USA) and then exported into SPSS software, Version 11 (SPSS, Inc., Chicago, IL, USA) for further analysis. Independent *t* test was used to determine statistical significance of age and kidney length, the Mann-Whitney test was used for serum creatinine, and the χ^2 test was applied to population distributions. Multivariate regression analysis was performed to test for independent variables. A *P* value of 0.05 or less was selected for statistically significance. Errors are presented as standard errors.

Table 1. Patient characteristics

	Cyst	No cyst	*P* value
Total population	385	2141	
Age *year*	64.1 ± 0.8	54.5 ± 0.4	<0.0001
Males	251 (65%)	1174 (55%)	<0.0001
Outpatients	165 (43%)	731 (34%)	<0.001
Indications			
Acute renal failure	39%	53%	<0.0001
Chronic renal failure	41%	27%	<0.0001
Proteinuria	5.7%	6.6%	
Hematuria	3.4%	3.5%	
Other	11%	10%	

RESULTS

Characteristics of the patients are shown in Table 1. Patients with cysts were significantly older and significantly more likely to be male than patients without cysts. The incidence of cysts in male patients was 18% compared to 11% in women. A significantly greater proportion of the patients with cysts were outpatients, who overall had an incidence of cysts of 18% compared to 14% in inpatients. This may be related to the fact that outpatients were more likely to have chronic renal failure. In patients with cysts, approximately 40% of the sonograms were performed for chronic renal failure, and an equal proportion was performed for acute renal failure. Almost all of the latter were inpatient studies. This was significantly different than patients without cysts, in whom twice as many studies were performed for acute renal failure than for chronic renal failure, suggesting that the incidence of cysts is increased in chronic renal failure. It was assumed that underlying renal disease was present in all outpatients and in those inpatients whose indication for sonography was chronic renal failure. To determine the extent of chronic renal insufficiency in the remaining 159 inpatients with cysts, an attempt was made to ascertain the baseline serum creatinine value during the hospitalization. This was accomplished in 128 patients and the results are shown in Figure 1. Serum creatinine was ≤1.4 in 42 patients and ≤2.0 in 83 patients. It is likely that the true baseline creatinine concentration is lower than that during hospitalization.

The distribution of cysts is shown in Table 2. The majority of patients had a single cyst and in those with multiple cysts, 90 patients (24% of all patients with cysts) had bilateral cysts. Patients with solitary kidneys (14) were not included in this table. To determine whether sonography was accurately reflecting the number and distribution of cysts, we analyzed 100 of the inpatients with cysts and identified 20 in whom results of a computed tomography (CT) or magnetic resonance (MR) scan of the abdomen were available. Because most of the CT scans were performed without intravenous contrast, some cysts could not be definitively diagnosed as such. However, for the purpose of this analysis, all lesions on

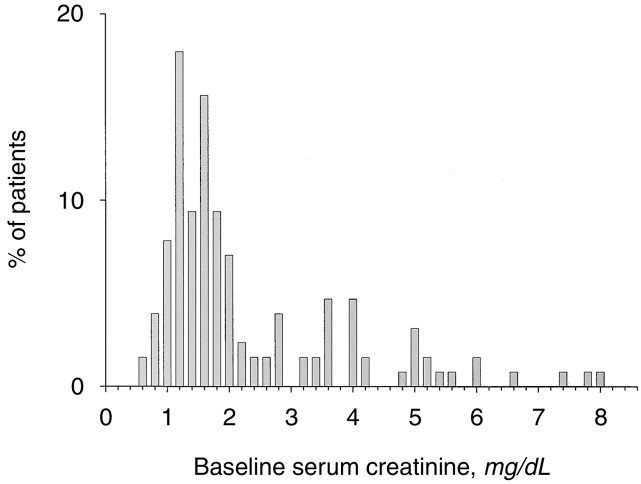

Fig. 1. Distribution of baseline serum creatinine concentration in hospitalized patients in whom sonography was performed for an indication other than chronic renal failure. Each bar indicates the percentage of patients whose serum creatinine concentration is no greater than the value for that bar but greater than the value for the previous bar. Total number of patients was 128.

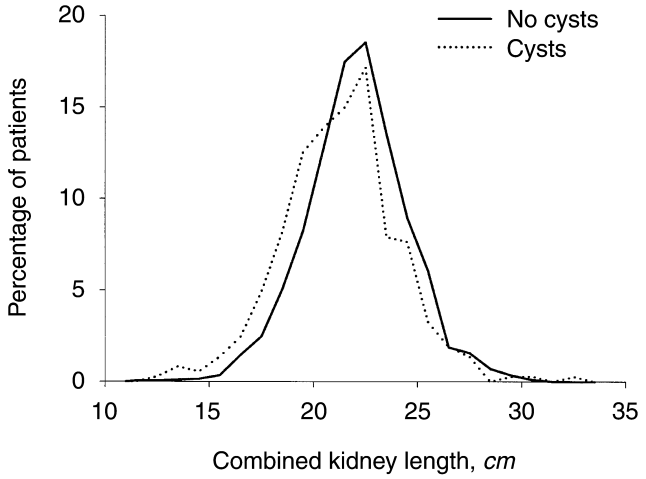

Fig. 2. Percentage of patients with and without cysts in each 1 cm increment of combined kidney length.

Table 2. Distribution of cysts

	Total cyst number		
Distribution	1	2	≥3
Right kidney only	137 (37%)	6 (1.6%)	7 (1.9%)
Left kidney only	114 (31%)	10 (2.7%)	7 (1.9%)
Bilateral		52 (14%)	38 (10%)
Total	251 (68%)	68 (18%)	52 (14%)

Table 3. Kidney lengths (cm) in patients with cyst and without cysts

Kidney	Cyst (N = 371)	No cyst (N = 2073)	P value
Right	10.4 ± 0.10	10.8 ± 0.03	<0.0001
Left	10.5 ± 0.10	10.9 ± 0.03	<0.0001
Right + left	20.8	21.6	<0.0001

Numbers of patients are given in parentheses.

Table 4. Lengths of involved (ipsilateral cysts) and uninvolved (contralateral cyst) kidneys in patients with cysts compared to kidney lengths in patients without cysts

	Ipsilateral cyst(s)	Contralateral cyst(s)	No cysts (N = 2073)
Right	10.4[a] (N = 240)	10.4[b] (N = 131)	10.8
Left	10.5[a] (N = 221)	10.6[c] (N = 150)	10.9

[a]$P < 0.0001$; [b]$P = 0.002$; [c]$P = 0.025$ vs. patients with no cysts

CT consistent with cysts were considered to be cysts. In 15 kidneys with a single cyst seen by sonography, CT or MR showed a single cyst in 11 and one additional small cyst in four. In 15 kidneys without any cysts by sonography, CT or MR showed a single cyst in three. Thus, it is unlikely that patients with single cysts on sonograms actually had multiple cysts. However, small cysts could have been missed in those patients who underwent unenhanced CT.

Both the length of the right kidney and the length of the left kidney, as well as the combined length, were smaller in patients with cysts and the difference was highly significant (Table 3). The reduction in combined kidney length was approximately 4%. Kidney size varies with body size but anthropometric data were not available on most of the patients. The kidney lengths in patients without cysts were similar to those reported for normal individuals without normalization for body size [8, 9]. Left kidney length was significantly greater than right kidney length (0.78 ± 0.02 cm, $P < 0.001$), consistent with previous studies [8, 9]. As revealed in the histograms shown in Figure 2, the distribution of renal lengths was the same in both groups, indicating that the smaller lengths in patients with cysts cannot be ascribed to a subpopulation of especially small kidneys.

The relationship between cysts and kidney length was explored further by comparing kidneys with and without cysts (Table 4). The data are separated by right and left kidney because of the normal difference in size. Kidneys with cysts were smaller than kidneys without cysts, and kidney length was also reduced in noncystic kidneys when cysts were present in the opposite kidney. Thus, the correlation between cysts and renal length is not limited to involved kidneys, suggesting that decreased renal mass might contribute to cyst development. This was examined in patients with solitary kidneys (Table 5). The proportion of patients with cysts was the same in patients with solitary kidneys and in patients with dual kidneys. However, when expressed per kidney, it was clear that solitary kidneys were significantly more likely

Table 5. The incidence of cysts in single and dual kidneys

	Dual kidneys	Solitary kidney	*P* value
All patients	2444	82	
Patients with cysts	371 (15%)	14 (17%)	0.32
Kidneys with cysts	469 (9.6%)	14 (17%)	0.01

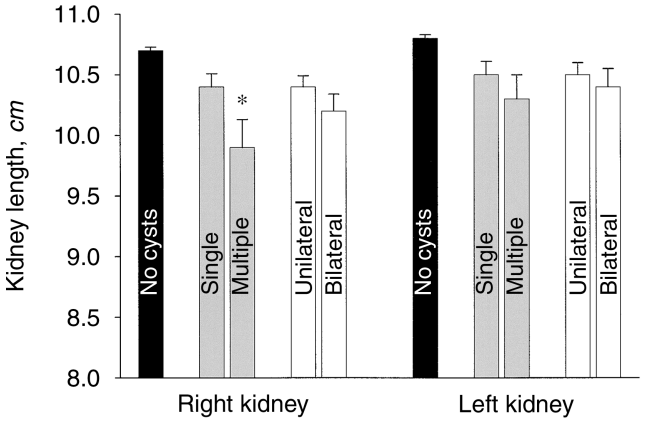

Fig. 3. Relationship between cyst number and distribution and renal lengths. Error bars indicate standard errors. *$P < 0.05$ vs. patients with solitary cysts.

to have cysts. Kidneys were smaller in patients with multiple cysts than in patients with solitary cysts, but the difference was only significant for right kidneys (Fig. 3). Kidneys were also smaller in patients with bilateral cysts than in patients with unilateral cysts but this difference was not statistically significant.

Because age, gender, and renal length were all significantly correlated with the presence of cysts, and because renal length is known to vary with age and gender [8, 9], a multivariate regression was performed to determine the independence of these parameters (Table 6). Age, gender, and combined kidney length were each highly significant, independent variables that together accounted for one third of the cyst occurrence. An additional analysis was performed to determine whether the reduction in renal size was associated with a reduction in renal function. Since it was likely that renal function was not stable or was not at baseline in many of the inpatients, this analysis was restricted to outpatients. These were patients referred to or followed in a nephrology clinic and thus had existing renal disease or hypertension. It is possible that acute renal failure was present in some, but its incidence should not differ between patients with and without cysts. Serum creatinine concentration was obtained by chart review of 143 outpatients with cysts and 143 patients without cysts matched for age and gender. As shown in Table 7, the mean serum creatinine concentration was greater in patients with cysts but the difference was of borderline significance.

Table 6. Multivariate analysis of the correlation between age, gender, and combined kidney length and the presence of renal cysts

	β	*P* value
Age	0.170	<0.0001
Gender	−0.071	0.001
Kidney length	−0.096	<0.0001

Table 7. Comparison of outpatients with kidney cysts to age-matched and gender-matched outpatients without cysts

	Cyst	No cyst	*P* value
Number	143	143	
Age *years*	62.9 ± 1.2	62.2 ± 1.2	NS
Gender *% males*	59	59	NS
Creatinine *mg/dL*	3.1 ± 0.2	2.6 ± 0.2	0.06[a]

[a] Mann-Whitney test, single-tailed

Data from 22 patients with cysts (13%) are not included because a serum creatinine value was not available within 3 months of the study. The median creatinine level was also increased in patients with cysts and the two groups had similar distributions of creatinine (not shown). The elevated creatinine levels reflect the prevalence of chronic renal insufficiency in this outpatient nephrology practice.

DISCUSSION

Renal length was significantly reduced in patients with one or more cysts in their kidneys. Sonographic measurements can be imprecise due to the dependence of the technique on the sonographer. In the case of renal length, the intraobserver and interobserver variabilities are approximately 5% [16, 17; Yuan Y, O'Neill WC, unpublished data] but it is unlikely that cysts would introduce any systematic bias in this error that would artifactually reduce the measurement of length. If anything, cysts would be expected to increase renal length. The additional measurements necessary to estimate renal volume were not available but renal volume was almost certainly reduced as well since length correlates fairly well with renal volume [8, 16]. It is unlikely that cysts would alter the relationship between length and volume. The reduced length of the noncystic kidney in patients with unilateral cysts demonstrates that the findings cannot be explained by an effect of cysts on kidney shape or measurement of length. The reduced length of noninvolved kidneys also suggests that total renal mass is the important parameter, which is consistent the observation that the sum of the lengths of both kidneys showed the greatest reduction in patients with cysts. Because cysts do not contribute to renal function, there is likely to be an even greater reduction in functional renal volume.

However, this conclusion will require verification with a more precise determination of renal volume.

These results suggest that reduced renal mass leads to cyst formation, but it is possible that renal size is merely linked to cysts but not causative. Age is one possible explanation for such a linkage since it was highly correlated with cysts and renal length decreases with age [6–9]. However, multivariate analysis revealed that age and renal length were both independently associated with the presence of cysts. Another possibility is that cysts are the result of underlying renal disease that also reduces renal mass and this cannot be addressed with the current data. However, the increased incidence of cysts in solitary kidneys is strong evidence for a causative role of reduced renal mass. Almost all solitary kidneys were the result of nephrectomy but the indication for the nephrectomy was often not recorded and therefore we cannot rule out the possibility that the cause of the nephrectomy is related to cysts. Renal tumors were probably the most common reason for nephrectomy but, aside from tuberous sclerosis and von Hippel-Lindau disease, they are not associated with cysts. Although patients with these genetic disorders were excluded, they can be unrecognized and the cystic involvement can be very mild [18]. Thus, it is possible that some of the patients with cysts and nephrectomy had one of these disorders.

Since cysts were detected by renal sonograms, all patients in this study had some type of renal abnormality. In hospitalized patients this was usually acute renal failure, which included ischemic acute tubular necrosis, acute drug toxicity, and prerenal azotemia. None of these conditions is associated with acute cyst formation, so any cysts would have predated the renal failure. Underlying renal disease cannot be excluded since it predisposes to acute renal failure. The bulk of the remaining sonograms were performed for chronic renal failure, and this indication was significantly more frequent in patients with cysts, suggesting that cysts are associated with poorer renal function. This is consistent with the observation that outpatients with cysts tended to have higher serum creatinine levels. Serum creatinine is not a precise indicator of glomerular filtration rate (GFR), but anthropometric data needed for more accurate estimates were not available in most patients. The accuracy of creatinine improves at the higher levels present in most of the outpatients and a further elevation in patients with cysts is certainly indicative of a poorer GFR. There is no reason to believe that patients with cysts have a larger body size that would explain the greater serum creatinine concentration. Because the bulk of patients undergoing outpatient sonography have chronic renal disease, it can only be concluded that cysts may be associated with poorer function in patients with renal disease. Additional studies will be needed to determine whether the same relationship holds in patients without apparent renal disease.

It is unlikely that the results were influenced by recognized cystic disorders of the kidney. Patients known to have genetic cystic diseases were excluded from analysis and care was taken to exclude undiagnosed cases. Any patient with multiple bilateral cysts and grossly enlarged kidneys or any patient with cysts and an affected parent were considered to have autosomal-dominant polycystic kidney disease. Very early cases of autosomal-dominant polycystic kidney disease could have been missed but the renal enlargement in polycystic kidney disease is contrary to the reduced renal size in the patients with cysts. Other genetic disorders such as tuberous sclerosis and von Hippel-Lindau disease are rarer and associated with renal neoplasms. ACKD, as it is currently recognized, cannot explain the results since only 24% of patients had bilateral cysts and only 14% had more than two cysts. Furthermore, this disorder occurs in dialysis patients or patients with very advanced renal failure. Patients undergoing chronic dialysis were excluded from the study and serum creatinine concentration, although elevated in patients with cysts, was not significantly greater than in patients without cysts (Table 7). Serum creatinine concentration was 2.0 or less in a substantial number of patients with cysts (Fig. 1). Although our patients did not have the form fruste of ACKD, the data support the possibility that this disease begins much earlier in renal failure.

The possibility that kidney cysts are the result of reduced nephron mass has not received much consideration beyond the identification of ACKD. The etiology of simple cysts is unknown but likely involves aberrant tubular growth [11]. It is likely that reduced renal mass increases the workload of existing tubules resulting in a hypertrophic response [10] that could predispose to this aberrant growth. A previous report documenting an association between reduced renal function and microscopic cysts in renal biopsies [19] lends support to this hypothesis. However, it remains to be determined whether these microcysts are the predecessors of simple cysts observed by sonography. The incidence of cysts also increased with age, and renal volume decreases with age [6–9], suggesting a possible link. However, multivariate analysis revealed that each was an independent determinant of cyst prevalence. The increased incidence of cysts in males, which is consistent with previous reports [1, 3–5], was also independent of renal length. This was expected since kidney size is greater in males due to increased body size [1, 3–5] while kidney size was reduced in patients with cysts. The mechanism that underlies this male predisposition is unknown but may be related to a greater underlying growth stimulus that also accounts for the increased prevalence of acquired cystic disease and renal carcinoma in males [14, 15]. Together, age,

gender, and kidney length accounted for only 33% of the incidence of renal cysts. This percentage may increase with more accurate measurements of renal volume such as CT or MR imaging, which are also more sensitive at detecting cysts. Despite the limitations of sonography, it is clear that cysts, even as few as one, are associated with reduced renal size in patients undergoing renal sonography. Since these patients had some type of renal abnormality that led to sonography, it can only be concluded that this relationship exists in patients with renal disease or abnormalities. The fact that many patients with cysts had chronic renal failure also suggests that the reduced renal size in patients with cysts represents very early acquired cystic kidney disease. Whether the relationship between cysts and kidney size exists in individuals without overt renal disease is an important question that requires further study.

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